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Editorial Comment

Disease-Causing Polymorphisms in the Spectrum of Long QT Syndrome Mutations*

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Long QT syndrome (LQTS) exemplifies many of the complexities of the genetic basis of disease. Mutations of different genes can cause a similar phenotype. Identical mutations can give rise to variable phenotypes. Obvious phenotypes can elude detection of an underlying genetic abnormality. Common, "benign" genetic variations can cause disease.

After discovery that mutations in several genes could cause congenital LQTS (1–4), and that many individuals with these mutations displayed negligible QT prolongation (5,6) ("silent LQTS"), it was postulated that drug-, bradycardia-, or electrolyte-induced "acquired" LQTS might represent unmasking of the LQTS phenotype in people with silent underlying LQTS mutations. As Roden (7) has articulated in the repolarization reserve hypothesis, multiple challenges to the myocyte's repolarization mechanisms may be required to produce clinical QT-interval prolongation. Studies seeking confirmation of a genetic predisposition revealed LQTS mutations in a minority of patients with acquired LQTS, as well as a disproportionately high prevalence of certain LQTS gene polymorphisms (8–15).

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One of these genetic variants was the *KCNE1* polymorphism D85N, which Paulussen et al. (13) found in 5% of patients presenting with torsades de pointes after receiving QT-interval–prolonging drugs (but in 0% of controls in that study) (13). This polymorphism has been detected in 0.7% of an Asian population (16). The *KCNE1* polymorphism encodes the beta-subunit of the I_{Ks} channel (17) and also interacts with *KCNH2*, which encodes the alpha-subunit of the I_{Kr} channel (18), although *KCNE1/KCNH2* interactions in native cardiomyocytes are not firmly established. Mutations in *KCNE1* can cause LQT5.

In this issue of the *Journal*, Nishio et al. (19) report finding 23 D85N heterozygotes and 1 homozygote among 317 LQTS probands screened, to yield an allele frequency of 3.9%, compared with 0.81% in healthy controls. After excluding 7 probands with additional mutations in LQTS genes and 3 women with "predisposing factors" (drug exposure, electrolyte disorder, or bradycardia), the allele frequency was 2.1%. The LQTS probands with the D85N variant had a milder phenotype than probands with other LQTS mutations: shorter mean QT interval corrected for heart rate (QTc) (507.9 ± 9.2 ms vs. 540.6 ± 6.1 ms) and older age at onset of symptoms (35.5 ± 10.4 years vs. 21.0 years). Nevertheless, 6 of the 13 patients with only D85N detected had syncope and/or documented torsades de pointes and QTc ranged as high as 650 ms. Based on these compelling findings, D85N appears to be a disease-causing genetic variant.

Nishio et al. (19) further demonstrated in mammalian cells that D85N reduced *KCNQ1*-encoded currents by 28% (previous experiments in *Xenopus* oocytes had shown a 50% reduction) (20). Moreover, D85N reduced *KCNH2*-encoded currents by 31% to 36%. Thus, the investigators reason, mutations in *KCNE1* may cause clinical features similar to those seen in LQT2. In fact, 3 of the D85N carriers in the current study had sinus bradycardia (as can be seen in LQT2).

The requirement for multiple repolarization challenges to unmask the phenotype in a substantial subset of the D85N subjects, as well as the older age of onset of symptoms and the shorter mean QTc interval as compared with probands with other LQTS mutations, point to a generally milder LQTS phenotype in D85N carriers. On the other hand, D85N is likely clinically important, especially in older individuals, who remain at risk of torsades de pointes (21) and whose exposure to bradycardia, electrolyte disorders, and QT-interval–prolonging drugs increases with age.

It was long assumed that polymorphisms were benign—after all, they are relatively prevalent in healthy populations. We now know from other studies that polymorphisms can worsen or improve the phenotype in the presence of disease-causing mutations (22,23), or even, as Tan et al. (24) showed, cause disease in the presence of a second (splicing) genetic variation. The current study (19) shows

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that the D85N polymorphism can itself cause disease and should more appropriately be classified as a mutation.

It is becoming increasingly clear that we cannot define health or disease by mutation status alone. An asymptomatic individual without QT interval prolongation, found during family screening to carry a known "disease-causing" mutation, is at much lower risk than a patient who presents with syncope, torsades de pointes, and marked QT interval prolongation in the absence of drug exposure or electrolyte disturbance, and whose genetic testing reveals only "benign" polymorphisms. Even as genetic testing becomes more sophisticated, there is still a critical role for clinical evaluation and risk profiling.

This is not to minimize the value of genetic testing. Knowledge of gene status in LQTS family members with a borderline phenotype, and determination of LQTS subtype in patients with a clear phenotype, directly inform decisions about evaluation and follow-up. Results of genetic evaluation, appropriately incorporated into a more comprehensive clinical evaluation and risk assessment, can save lives, improve quality of life, reduce inappropriate and potentially risky interventions, and conserve medical resources. Furthermore, if widespread genetic surveys become practical within the normal-phenotype population, awareness of underlying polymorphisms, such as D85N, could point to potential repolarization vulnerability and guide therapy away from known QT-interval–prolonging drugs. Additional well-executed studies like that of Nishio et al. (19) may advance us further in that direction. Until then, the clinician must resort to standard strategies such as monitoring the QT interval and avoiding combinations of QT-interval–prolonging and electrolyte-disturbing drugs.

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Key Words: long QT syndrome ■ single nucleotide polymorphism ■ disease-causing variant.